REMARKS/ARGUMENTS

In reply to the Advisory Action mailed December 21, 2004, Applicants have corrected clerical errors pursuant to the Examiners comments (i) – (iv) in the continuation sheet of the action whereby it is believed that the present amendment is in compliance with 37 C.F.R. 1.121(c).

Reconsideration of this application in view of the foregoing amendments and the following remarks is respectfully requested.

With this amendment, claims 2, 3, 5, 6, 19, and 20 remain in the application. Claims 35-42 are newly submitted herein.

i. The rejection under 35 USC 102(b)/103(a) in view of McCormick

In the action, the Examiner has applied U.S. Patent No. 4,760,017 of McCormick against claims 2-6 and 19-20 as being anticipated or obvious over McCormick. The Examiner indicates that McCormick describes arabinonucleic acid and the use of a polynucleotide probe in the DNA or RNA hybridization assays. The Examiner has also noted that β-D-arabinonucleosides are used in the synthesis of the arabinonucleoside probes of McCormick. The Examiner also states that although the McCormick reference does not specifically teach that that the arabinonucleic probes can be used to induce RNaseH activity, the probes of this reference meet all of the structural limitations of Applicant's invention, particularly wherein it is drawn to an olgonucleotide consisting of β-arabinose sugars hybridizing to a single stranded RNA. Reconsideration on the following grounds by the Examiner is respectfully requested on the following grounds.

Claims 2 and 19 have been presently amended to specify that the claimed oligonucleotide compositions selectively prevent or modulate gene expression in a sequence-specific manner in a host, support for which can be found at page 17, lines 15-21 of the instant application. Claims 2 and 19 have also been presently amended to claim compositions comprising at least one of an oligonucleotide consisting of β-D-arabinose sugars hybridizing to complementary RNA to induce RNase H activity, an oligonucleotide consisting of β-D-arabinose sugars substituted at the 2' position of the sugar rings with various specified substituents and hybridizing to complementary RNA to induce RNase H activity, and an oligonucleotide consisting of β-D-arabinose sugars substituted at the 2' position of the sugar rings with halogen, alkyl, alkylhalide, alkylsulfhydryl, allyl, amino, aryl, alkoxy, or azido and hybridizing to duplex

DNA/DNA or DNA/RNA to form a triple helical complex. These amendments are fully supported by the specification, for example at page 21, line 12 through to page 23, line 15, and page 22, lines 26-30 of the instant application, as well as claims 1 and 2 as originally filed in the instant application during the international phase. Support for use of the term "complementary" when referring to RNA in the presently amended claims can be found at page 22, lines 17-2 of the instant application, and in claim 4, which has presently been cancelled.

Claim 2 has also been amended to more clearly indicate that all claimed oligonucleotide compositions are in association with an acceptable carrier.

The language of claim 3 and claim 20 has been amended to further clarify the structure of the sugar rings of the claimed oligonucleotides as being 2'-difluoro-substituted, support for which can be found at page 17, line 22 through to page 18, line 21 of the instant application.

New claims 35 through 42 have been added to further define preferred embodiments of the oligonuclotides and compositions comprising oligonucleotides of Applicant's instant invention. In particular, Applicant has added oligonucleotide claims 40-42 that correspond to composition claims 35, 38, and 3, respectively in order to fully claim Applicant's instant invention.

The dependency of claims 5 has been amended to depend from claims 2 and 3.

Claims 31-34 have been cancelled without prejudice.

The amendments to the present claims and newly submitted claims are supported by the instant application and do not present new matter.

Reconsideration by the Examiner is respectfully requested on the following grounds.

Applicant respectfully submits that there is no teaching of compositions of arabinonucleosides or derivatives thereof, including the presently claimed oligonucleotides consisting of β-D-arabinose sugars unsubstituted or substituted at 2' position of the sugar ring, for the purpose of binding RNA to elicit RNaseH activity in the reference of McCormick. Rather, McCormick teaches arabinonucleosides (ANA) can be used as probes for single-stranded DNA or RNA in the *in vitro* analysis of samples, for example, see column 3, lines 49-58. McCormick also teaches at column 3, line 59 onwards that nucleic acids to be analyzed have many sources, including clinical specimens and various microorganisms, and teaches that

(our emphasis), "Extraction is one common method for collecting the nucleic acid from their source for hybridization assays. The protocol for use of the ANA probes of this invention is much like that in conventional hydridization procedures. The target DNA or RNA is first rendered single-stranded and then immobilized onto a support. The immobilized single-stranded nucleic acids are then treated with the arabinonucleic acid probe complementary to a sequence of bases in the target." Also, as is taught in Applicant's instant application, the cellular enzyme RNaseH is known to degrade RNA of a DNA/RNA heteroduplex, and page 14 of Applicant's instant application teaches that while HIV-1 reverse transcriptase (RT)-associated RNaseH has been shown to cleave both DNA/RNA and RNA/RNA duplexes, cleavage of the latter is at least 30-fold slower and occurs only when RT is artificially arrested. Given that McCormick teaches the preparation of both single-stranded DNA and RNA, the compositions of McCormick do not necessarily teach in every instance the formation of duplexes with arabinonucleoside probes that could induce RNaseH activity, i.e., the preparation of DNA/RNA heteroduplexes.

Moreover, it is respectfully submitted that there is no explicit teaching or suggestion in McCormick that RNaseH should or would necessarily be present in the in vitro compositions containing the immobilized single-stranded nucleic acids and arabinonucleoside probes for *in vitro* analysis subsequent to the extraction and immobilization process of McCormick. Moreover, even if there were, as an artifact of the extraction and immobilization process of McCormick, a sufficient quantity of RNaseH incidentally present in a composition of McCormick containing immobilized single-stranded RNA, and that RNaseH were able to catalyze the degradation of the immobilized single-stranded RNA, it is respectfully submitted that the activation of such catalytic activity would destroy the intended functionality of McCormick's arabinonucleic acid probes. Once an arabinonucleoside probe would bind to the RNA, the resulting hybrib would be a substrate for RNaseH present in solution, resulting, in turn, in degradation of the bound RNA strand into smaller fragments. Cleavage of the bound RNA into smaller fragments would clearly destroy the intended functionality of the invention of McCormick which is the use of arabinonucleic acid probes in DNA and RNA hybridization assays for the subsequent identification of such DNA or RNA. As is described at column 3, lines 50 through to column 4, line 25 of McCormick, the successive washings to remove any unbound arabinonucleoside probe would likely likewise wash away the RNA degradation products and would not afford an immobilized RNA-ANA hybrid for subsequent labeling with an anti-arabinose antibody-label conjugate as is clearly intended.

Moreover, Applicant respectfully submits that there is nothing in McCormick that directly evidences the presence of RNaseH in the compositions of McCormick, nor are there working examples that evidence the formation of RNA-ANA duplexes eliciting RNase H activity. If a prior art reference does not expressly set forth a particular element in the claim, the reference may still anticipate if the element is inherent in the disclosure. However, to establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the reference, and that it would be so recognized by persons of ordinary skill. Inherency may not be established by probabilities or possibilities, and the mere fact that a certain thing may result from a given set of circumstances is not sufficient (*Continental Can Co. v. Monsanto Co.*, 948, F.2d 1264, 1268, 20 U.S.P.Q.2d 1746, 1749 (Fed. Cir. 1991); *In re Orlrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326, (C.C.P.A. 1981). Given that there is no evidence that McCormick does not teach in every instance RNA-ANA duplexes that could elicit RNase H activity as is claimed in the present amended claims, Applicant respectfully submits that the present claims are novel in view of McCormick.

Moreover, Applicant respectfully submits neither McCormick nor any other prior art has taught or suggested the use of antisense ANA's for cleaving hybridized RNA by RNase H as is claimed in the present invention. Until the instant invention, there were no known examples of uniformly *sugar-modified* oligonucleotides that elicited RNaseH activity upon association with a target RNA. Pages 9 through 20 of the instant application describes that only DNA-based oligomers (i.e., those containing 2-deoxyribose) were known in the prior art to elicit RNase H activity. This is primarily because the enzyme normally processes DNA/RNA hybrids (not RNA/RNA duplexes); and the activity/specificity of RNase H is extremely sensitive to structural changes made to the heteroduplex (e.g. modifications made to the sugar-phosphate backbone of the antisense DNA or target RNA strand). In fact, of the 60 types of modified oligomers studied during the period 1994-97 in the prior art, none apart from DNA-based oligos (PS-DNA and PS-DNA gapped oligos) were reported to activate RNase H (see review article by Sanghvi, Y. In *Comprehensive Natural Product Chemistry*; Barton, D. H. R., Nakanishi, K., Meth-Coth, O., Eds.; Elsevier Science: Oxford, UK, 1998). Thus, Applicants' discovery that a 2'-modified oligomer (such as 2'-OH or 2'F-arabinose) was capable of eliciting RNase H was totally unexpected. Therefore, the presently claimed oligonucleotides, such as oligonucleotides consisting of arabinose sugars (ANA with 2'OH groups), 2'-substituted β-D-arabinose sugars such as FANA (2'F), and 2'-difluoro-substituted sugars of the present invention represent the first examples of uniformly sugar-modified oligonucleotides that elicit RNase H activity. Applicant respectfully submits this is further evidenced by various scientific

articles that evidence the surprising invention, e.g., as described in Oliver Seitz, Angew. *Chem. Int. Ed.* **1999**, 38, 23, 3466-3469; Jens Kurreck, *Eur. J. Biochem.* **270**, 1628-1644 (**2003**); and Lisbet Kvaerno and Jesper Wengel, *Chem. Commun.* **2001**, 1419-1424, copies of which are being submitted with the present response for consideration by the Examiner.

As such, Applicant respectfully submits that one of skill in the art would not have considered obvious the compositions containing the presently claimed oligonucleotides to elicit RNase H activity to selectively prevent gene expression in view of McCormick or any prior art reference made of record.

Moreover, Applicant respectfully submits that the oligonucleotides of McCormick do not fall within the Applicant's presently claimed oligonucleotides or compositions of Applicant's new claims 35-42. As such, Applicant respectfully submits that the oligonucleotides do not fall within the instant claimed invention in claims 35-42, and thus McCormick is not anticipatory with respect to these claims.

In view of the foregoing, Applicant respectfully submits that claims 2, 3, 5, 6, 19, 20, and 35-42 are directed to subject matter that is inventive and novel in view of McCormick and respectfully submit that the Applicants were the first to show the use of an oligonucleotide based on arabinose sugars for cleaving RNA via RNaseH activation. None of the prior art teaches or suggest the present invention. Withdrawal of the novelty and obviousness rejection is accordingly respectfully requested.

ii. The rejection under 35 USC 103(a) over Cheng et al. in view of Chu et al. and Meyer et al.

In the action, the Examiner has maintained the rejection in respect of claims 2-6 and 19-20 under 35 USC 103(a), and has rejected claims 31-34 under 35 USC 103(a) as being unpatentable over Cheng et al. (US Patent No. 5,646,126) in view of Chu et al. (US Patent No. 5,808,040) and Meyer et al., (US Patent no. 5,177,196) for the reasons set forth in the Official Action dated September 25, 2003.

Reconsideration of amended claims 2, 3, 5, 6, 19, and 20 and new claims 35-42 by the Examiner is respectfully requested on the following grounds.

The reference of Meyer et al. discloses novel oligonucleotide compositions formed from α-D-arabinofuranosyl nucleoside monomers. These oligonucleotides are disclosed as being useful as

chemotherapeutic agents to control the expression of gene sequences or to inhibit mRNA translation. Meyer et al. does not disclose oligonucleotide compositions formed from β-arabinose units as is presently claimed, nor would it have been obvious to one having ordinary skills in the art, at the time of the invention, to arrive to the present invention from the teaching of Meyer, Jr. et al since it does not comprise any incentive to prepare oligonucleotide composition formed from β-arabinose units.

The reference of Chu et al. teaches a method for stabilizing oligonucleotides by including 2'-deoxy-2'-fluoro-arabinofuranosyl nucleosides into the oligonucleotides. Additionally, the reference of Chu et al. teaches that 2'-deoxy-2'-fluoro-β-L arabinosyluridine is a potent antiviral agent against HBV and EBV. The Examiner has indicated in the Official Action mailed June 30, 2004 that Applicant's claims do not recite that the arabinonucleoside units are 'D-nucleotide" units, as set out in Applicant's response filed April 8, 2004. Applicant has presently amended the claims to indicate that the oligonucleotides of the present invention are D-oligonucleotides comprised entirely of D-arabinonucleotide units. It is Applicant's respectful assertion that Chu et al does not disclose oligonucleotide compositions formed from β-D-arabinose units as is presently claimed, but rather consistently teaches the use of the incorporation of L-nucleosides in an oligonucleotide due to their stability against nucleases. Applicant likewise respectfully submits that it would not have been obvious to one having ordinary skills in the art at the time of the invention from the teachings of Chu to arrive to the present invention from the teaching of Chu et al., since Chu does not provide any incentive to prepare oligonucleotide composition formed from β-D-arabinose units, in place of those with L-stereochemistry, given that it would be understood by one of skill in the art that it is the unnatural L-configuration of the nucleosides of Chu confers stability to the nucleosides against nuclease degradation.

The reference of Cheng et al. describes oligonucleotides comprising 2'-deoxy, 2'-fluoro or 2'-difluoro nucleosides, wherein between 8 and 18 of said nucleosides are linked consecutively. Additionally, Cheng et al. teach that ODNs (oligonucleotides) including α and β arabinosides are included within the scope of the invention. Cheng et al. does not specifically disclose isolated oligonucleotides comprising arabinose sugars and 2'-fluoro or 2'-difluoro modified nucleosides consecutively linked in the same molecule.

The Examiner states that absent evidence to the contrary the skilled artisan would expect that if a portion of the molecules of Cheng et al. comprised a sequence that is complementary to a target RNA

sequence, these molecules would interact with cellular RNA and form a complex. Applicant respectfully submits that throughout the reference of Cheng et al. is disclosed the synthesis and use of duplexes (not single stranded oligomers) which by virtue of their duplex structure are endowed with anticancer properties. In the Summary of the Invention at Column 5, lines 18-24, Cheng et al. states the following (our emphasis):

> *"It has been discovered in accordance of the present invention that the stable duplex oligonucleotides which have the structures described above in the Summary of the Invention and shown in FIG. 1 have significant selective cytotoxic activity against certain cancer cell lines, including some cancer cell lines which have resistance to several established anticancer agents."*

Thus, Applicant respectfully submit that the mechanism of action intended by the inventors is not antisense, i.e. preventing or modulating gene expression in a sequence-specific manner as it is the case for the composition of the claimed invention. This is further described explicitly by Cheng *et al.* at column1, line 59-61 through to column 2, lines 14-19 as follows (our emphasis):

> *"To this date however, results with antisense oligonucleotides (ODNs) have been somewhat disappointing in terms of successful chemotherapy ... As far as the present inventors are aware, the present invention provides, for the first time, modified oligonucleotides which show anticancer activity in other than an "antisense" manner, and which show selective toxicity toward certain cancer cell lines, and to certain cancer cell lines with multiple drug resistance."*

Likewise, it is the Applicant's respectful assertion that the oligomers of Cheng et al. are clearly described as and designed to be self-complementary (for example, see the ODN of Figure 5 which is described at column 7, lines 27-34 as being capable of forming substantially stable duplexes with itself and corresponding to type 1 oligomers of the invention of Cheng) in order to promote self-hybridization and duplex formation. Moreover, some of the oligomers of Cheng et al. are described as being designed to fold back upon themselves to form a hairpin structure (for example, see Figure 1, type 3). The aliphatic linkers of Cheng et al. ("hairpin turns") shown in Figure 14 are described as facilitating folding and hairpin formation. Moreover, Cheng et al. notes that when the sequence of the

oligonucleotide was designed so that an imperfect duplex would form (e.g., only 8 bp of potentially 10 bp) biological activity was compromised (e.g. see column 8, lines 18-35). Column 8, lines 34-39 of Cheng et al. likewise emphasizes the requirement of the duplex structure in the ODNs of Cheng et al. and column 8, lines 36-64 of Cheng et al. provide data suggesting that the most active compounds are the most stable duplexes, whereas the inactive compounds exist as single strands. Gel electrophoresis data was used to support this conclusion (see Figure 7 of Cheng et al.).

Applicant has noted that several of the references listed on the covering page of Cheng et al. relate to "decoy" nucleic acids, which are also referred to in the art as "aptamers". Aptamers are known to those of skill in the art to generally refer to duplexes which are capable of binding proteins and, as such, serve as "sinks" by blocking the protein from further function. For proteins involved in cellular signaling, a specific aptamer duplex interaction could ultimately modulate expression of the respective gene(s) in that pathway. On the other hand, if the aptamer duplex binds a viral protein, it might inhibit further proliferation and/or infectivity, thereby serving as a potent antiviral agent. The latter approach is the one pursued in the work by Ma et al. – which is cited under "other publications". Here RNA duplexes are designed to bind and inhibit HIV-1 viral proteins (tat). A similar approach is described by Bielinska et al., also cited under "other publications". Applicant respectfully submits that these approaches are very different from the antisense approach whereby a single stranded oligomer (not duplex) is designed to bind to mRNA (not a protein).

Applicant respectfully submits that one having ordinary skills in the art to which the invention pertains would readily understand that the oligomers of Cheng et al. are meant to be duplexes, and would not have been lead to modify the invention of Cheng et al. with the method of Chu et al., to arrive to the present invention since our oligonucleotides provide activity in an "antisense" manner, i.e. their base sequence is designed so that they (a) remain as single strands (not duplexes), and (b) are reverse complementary to the sense RNA target.

The amendments to claims as presented above are believed to overcome the Examiner's rejections under 35 U.S.C. 103(a).

No new matter is entered.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested.

The Examiner is authorized to charge fee deficiencies or credit overpayments to the NIXON PEABODY LLP Deposit Account No. 50-0850.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Date: 3/3/05

Respectfully submitted,

David S. Resnick (Reg. No. 34,235)
NIXON PEABODY LLP
100 Summer Street
Boston, MA 02110
(617) 345-6057